Managing Anti-Platelet Therapy in Thrombocytopaenic Patients with Haematological Malignancy

Managing Anti-Platelet Therapy in Thrombocytopaenic Patients with Haematological Malignancy: A Multinational Clinical Vignette-Based Experiment

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Abstract

Data on anti-platelet therapy (APT) for prevention of atherothrombotic events in thrombocytopaenic cancer patients is lacking. We aimed to identify patient and physician characteristics associated with APT management in thrombocytopaenic patients with haematological malignancy. A clinical vignette-based experiment was designed. Eleven haematologists were interviewed, identifying five variable categories. Next, 18 hypothetical vignettes were generated. Each physician received three vignettes and chose to: hold all APT; continue APT without platelet transfusion support; or continue APT with platelet transfusion support. The survey was distributed to haematologists and thrombosis specialists in three countries. Multivariate cluster robust Poisson regression models were used to calculate relative risks (RRs) of using one management option (over the other) for each variable in comparison to a reference variable. A total of 145 physicians answered 434 cases. Clinicians were more likely to hold APT in case of 20,000/μL platelets (vs. 40,000/μL; RR for continuing: 0.82 [95% confidence interval: 0.75–0.91]), recent major gastrointestinal bleeding (vs. none; RR 0.81 [0.72–0.92]) and when the physician worked at a university-affiliated community hospital (vs. non-academic community hospital; RR 0.84 [0.72–0.98]). Clinicians were more likely to continue APT in ST elevation myocardial infarction with dual APT (vs. unstable angina with single APT; RR 1.31 [1.18–1.45]) and when there were

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institutional protocols guiding management (vs. none; RR 1.15 [1.03–1.27]). When APT was continued, increased platelet transfusion targets were used in 34%. In summary, the decision process is complex and affected by multiple patient and physician characteristics. Platelet transfusions were frequently chosen to support APT, although no evidence supports this practice.

Introduction

In an aging population, both ischaemic cardiovascular diseases (myocardial infarction [MI], ischaemic stroke) and cancer are increasingly prevalent.[1,2] Thus, the use of antiplatelet therapy (APT), prescribed for acute and chronic ischaemic arterial disease, is frequently encountered in cancer patients.[3] APT following acute atherothrombotic events and dual APT (DAPT) in particular, puts patients at a substantial risk of bleeding.[4–6] Patients with active malignancy undergoing anti-cancer treatment also have episodes of thrombocytopaenia of variable duration and intensity.[7] Chemotherapy-induced thrombocytopaenia poses a substantial risk of bleeding,[8] which is compounded by the irreversible effects of APT, in patients requiring APT.

At the same time, patients presenting with active cancer have an increased risk of atherothrombotic events as well as adverse outcomes.[9,10] Importantly, thrombocytopaenia ($<$ 50,000–100,000/μL) does not provide protection against arterial thrombosis.[11] In fact, thrombocytopaenia is associated with adverse short- and long-term cardiovascular outcomes and mortality in patients with and without cancer who have ischaemic heart disease (IHD) or stroke,[11–13] making this a high-risk population.

Generally, patients with thrombocytopaenia are excluded from clinical trials of APT.[14] Although there are several large cohort studies evaluating outcomes in IHD patients with thrombocytopaenia outside the context of malignancy, there are scarce data to guide management as recently reviewed by McCarthy et al.[13] Management in the context of cancer is informed only by small retrospective studies on aspirin in acute coronary syndrome (ACS), since it is difficult to recruit patients in interventional studies assessing management in this setting.[15] These cohort studies suggest that aspirin increases survival, without increasing bleeding.[12,16] Consequently, formal IHD and stroke guidelines do not provide recommendations for the management of thrombocytopaenic cancer patients,[17–19] with the exception of a consensus statement by the Society for Cardiovascular Angiography and Interventions (SCAI). The SCAI proposed aspirin administration with platelet counts above 10,000/μL in patients with ACS and percutaneous coronary intervention (PCI), and reserved DAPT for counts above 30,000/μL[20]; however, there is no evidence to support or refute the appropriateness of these thresholds.

Little is known about current practice in this setting. First, retrospective cohort studies suggest that aspirin is often not utilized in thrombocytopaenic cancer patients with ACS.[12,16] Second, in a recent French survey ($n = 98$), physicians reported re-assessing the benefits and risks of APT at varying platelet thresholds (~42% at 50,000/μL; ~24% at 30,000/μL; ~12% at 20,000/μL), while approximately 11% did not consider platelet counts.[21] However, this survey does not account for effects of other clinical variables on management choice and does not investigate different management strategies.

Understanding current practice will suggest whether physicians are able to deal with the practical challenges in a reasonable and uniform manner, in the absence of supportive evidence and/or clear and consistent guidelines. If detected, variability in practice could emphasize the need for better evidence and recommendations. Current practice may also instruct us which factors to address in future studies and guidelines. Therefore, we aimed to identify the patient and physician characteristics associated with APT management in patients with thrombocytopaenia and haematological malignancy.

Methods

Design

Vignette Experiment

A clinical vignette-based experiment was designed to mimic the clinical scenarios in which decision-making occurs, whereby each vignette represented a fictitious but realistic patient.[22] We employed a methodology similar to that used by Ten Cate et al as detailed in their study protocol.[23] Our population of interest was adult patients with haematological malignancy (due to a high incidence of thrombocytopaenia and bleeding[7,8]), who have disease or treatment-related thrombocytopaenia and any indication for APT.

Creating the Vignettes

Eleven haematologists in Israel and the Netherlands were interviewed and asked the following: 'which variables influence your management of anti-platelet medication in these patients?'; 'which management strategies would you consider?'. The variable list was refined based on a literature review and the number of times a given variable was mentioned across the interviews (minimum = twice), resulting in five attributes (i.e. variable categories) potentially influencing the management of APT, each with two to three levels (representing the actual variables) as shown in ►**Fig. 1A**. For instance, one of the five attributes was 'time since the anti-platelet indication-defining event' and the corresponding levels were '2 months' or '2 weeks'. Using computer algorithms, as previously described,[23] a balanced set of 18 variable combinations (i.e. case vignettes) was selected, as depicted in ►**Supplementary Table S1** (available in the online version).

A: List of selected attributes and levels

Attribute	Level 1 §	Level 2	Level 3
Haematological malignancy and treatment ¶, ‡	• Diffuse large B cell lymphoma • R-CHOP treatment	• ALL • Asparaginase-based chemotherapy	• AML • High dose cytarabine consolidation
Depth of thrombocytopaenia	40,000/μL	20,000/μL	
Indication and type of antiplatelet regimen ¶, †	• Unstable angina (no stent) • Single antiplatelet	• Ischemic stroke • Single antiplatelet	• STEMI with drug eluting stent • Aspirin & clopidogrel
Time since the antiplatelet indication-defining event	2 months	2 weeks	
Major GI bleeding from an unidentified source	Never	4 months earlier	3 weeks earlier

B: Case vignette examples

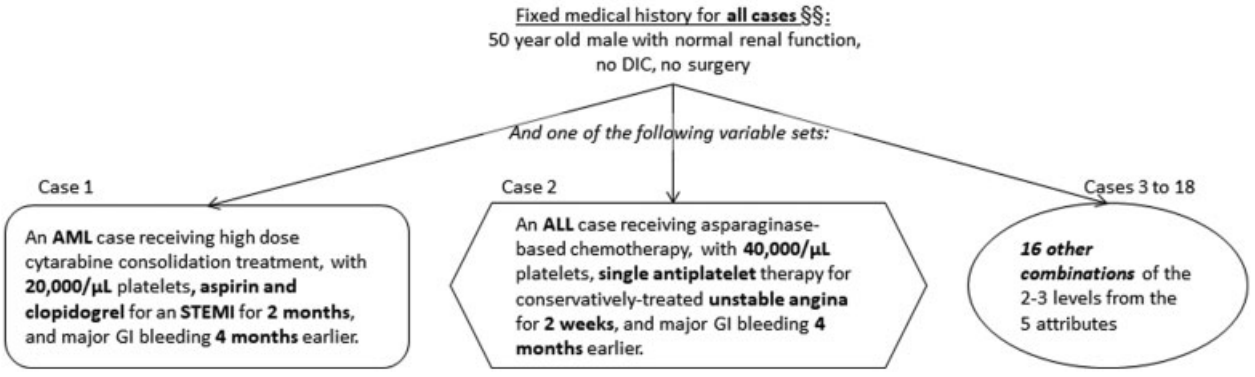


Fig. 1 The attributes and levels that were selected for evaluation in this study (panel **A**) and how case vignettes were built from these variables (panel **B**). In panel A, attributes represent the variable category (e.g. platelet count) while the levels are the actual variables (e.g. 20,000/μL or 40,000/μL). Each of the 18 selected case vignettes comprised one level from each of the 5 attributes. Panel B shows that all cases comprised a shared set of case constants§§, as well as 1 of the 18 selected variable combinations. Case example 1 and 2 comprised the 5 levels marked by the rectangle and hexagon, respectively, in panel A. § Level 1 is the reference level for statistical comparisons within each attribute group. Levels with lower thrombotic or bleeding risk were chosen. ¶This is a composite attribute linking two individual attributes which depend on each other. This was done to prevent implausible variable combinations. ‡ This attribute is a composite of 'duration of thrombocytopaenia' (represented by type of disease and treatment) and 'drug-specific thrombotic risk'. † This attribute is a composite of 'type of anti-thrombotic treatment' and 'indication for anti-thrombotic treatment'. §§ Five additional attributes with single levels were chosen as case constants which comprised the fixed medical history for all cases, as shown here. These attributes were: age, sex, renal function, DIC and surgery. This was done to improve clarity for the physician and remove ambiguity over variables which could confound decision making. Abbreviations: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; DIC, disseminated intravascular coagulation; GI, gastrointestinal; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone; STEMI, ST elevation myocardial infarction.

This fractional factorial design retained sufficient information compared with the full factorial design (108 cases) as shown by a D-efficiency of 99.9% and a G-efficiency of 97.3% (►**Supplementary Fig. S1**, available in the online version). ►**Fig. 1B** depicts how these attributes and levels were used to create the case vignettes, and shows 2 of the 18 vignettes selected for this study. No implausible cases were identified when the survey was piloted in Italy.

The 18 vignettes were algorithmically sub-divided into 6 diagonal blocks of 3 vignettes each (►**Supplementary Table S1**, available in the online version), meaning that there were 6 survey versions (A through F). Each participant was randomly assigned one version and was required to select an anti-platelet management strategy and to assess bleeding and thrombotic risk on separate scales of 0 (negligible risk of bleeding/thrombosis) to 10 (highest risk), for each case. The primary management could be one of the following: (1) hold all APT; (2) continue APT, without platelet transfusion support; and (3) continue APT with platelet transfusion support. The term 'hold' meant temporarily or permanently stopping APT. In the cases with aspirin and clopidogrel DAPT, there was also an option to hold either aspirin or clopidogrel, with or without transfusion support. When platelet transfusion support was used, the physicians had to select a platelet transfusion target of either 30,000/μL or 50,000/μL. Protein pump inhibitors should be uniformly considered in patients continuing APT[13] and therefore were not given as a management option. No management options were reported to be missing during piloting or the study itself, supporting the appropriateness of this selection. The survey was designed as a Web site which included functionality enabling the responders to contact the study team. Missing data were prevented by way of design, whereby participants could not progress to the next case before all questions were answered. The above process is shown in greater detail in ►**Supplementary Fig. S2** (available in the online version).

Sample and Setting

The target physicians were haematologists, thrombosis specialists and specialists in transfusion medicine, in Israel, Italy and the Netherlands, who are often the case managers in this inpatient setting. This population was selected since we considered these physicians to be most likely to make the final management decision (possibly after consulting with other disciplines, such as cardiologists or neurologists). A

link to the survey Web site was distributed in Israel, the Netherlands and Italy via mailing lists of national haematology and/or thrombosis societies ($n = 886$). The survey was anonymous and voluntary, and no compensation was offered. Data on physician characteristics, practice setting and relevant practice patterns were collected from each physician prior to answering the vignettes.

Randomization and Blinding

The Web site assigned consecutive participants with sequential questionnaire versions (►**Supplementary Table S1**, available in the online version) in ascending order (A through F and again A through F, and so forth). The questionnaire could only be accessed once at each Internet protocol (IP) address, preventing manipulation of questionnaire allocation by the responders. The surveys were anonymous and the IP location was neither linked to the questionnaire data nor included in the data file. Therefore, the study investigators were blinded to allocation.

Statistical Analysis

For analysis, management choices were grouped to enable stepwise comparisons between two management strategies at each step, as detailed in the ►**Supplementary Material** (available in the online version) and ►**Fig. 2**. This resulted in the following management steps (A→ B [B.1] → C): step A, continuing any APT versus holding all APT; step B (for those continuing any anti-platelet regimen), platelet transfusion support versus no transfusion support; step C (for those continuing APT, with or without platelet transfusion support) in DAPT cases, holding either aspirin or clopidogrel versus continuation of DAPT. In addition, when platelet transfusion support was used, a 30,000/μL platelet target was compared with 50,000/μL (step B.1). A sensitivity analysis was performed on step B, by excluding the DAPT cases and analysing the cases with single APT only.

For steps A, B and C, Poisson regression models with cluster robust standard errors,[24] clustered on physician identifier (to accommodate the repeated measures design), were calculated to estimate the relative risks (RRs) and corresponding confidence intervals (CIs) for choosing one management option (over the other) for each physician or patient variable compared with the reference variable. Mixed effects binomial logistic regression models were computed for visualization of the thrombotic and bleeding risk scores in steps A and B, which differed by physician. In these models, random intercepts were specified for physician ID and random slopes for thrombotic or bleeding risk scores, to model inter-physician variance. Random effects were omitted from models when irrelevant, that is, when they were approximately equal to zero. Random slopes of the physician-assessed bleeding risk were incorporated in the final step A model, while both the physician-specific random intercepts and the random slope for thrombotic risk perception were included in the final step B model. Predicted probability plots, incorporating 15 curves representing physician choices by risk assessment equidistantly distributed across the full range of percentiles, were used to visualize the random components of these models. Management steps are also shown descriptively as the number of cases in which a specific management strategy was selected.

R (R Foundation for Statistical Computing, Vienna, Austria) version 3.4.1 was used for all analyses. The 'AlgDesign' package was used to create the fractional factorial design (i.e. the case vignettes). Cluster robust standard errors were generated with the 'sandwich' package. Mixed effects models were implemented using the package 'lme4'. Predicted probability plots incorporating random effects were visualized with the 'visreg' package. Statistical significance was set at a two-sided p-value of < 0.05.

Results

Sample

The survey was answered by 145 subjects, mainly from Italy (48), Israel (46) and the Netherlands (44), between March 21, 2017 and May 29, 2017. This represents 16% of the 886 physicians directly invited to participate in these countries. ►**Fig. 3** shows the distribution of participants across regions in each country, while ►**Supplementary Fig. S3** (available in the online version) graphically depicts the geographic distribution across cities, both using the IP addresses at which the questionnaires were answered. These figures show that physicians from 36 regions across the participating countries answered the questionnaire, most probably representing at least 36 medical centres. In each of the three target countries, the most responders came from the region where the medical centres leading this study were situated (Lombardy, Italy; Maastricht, the Netherlands; Tel Aviv District, Israel).

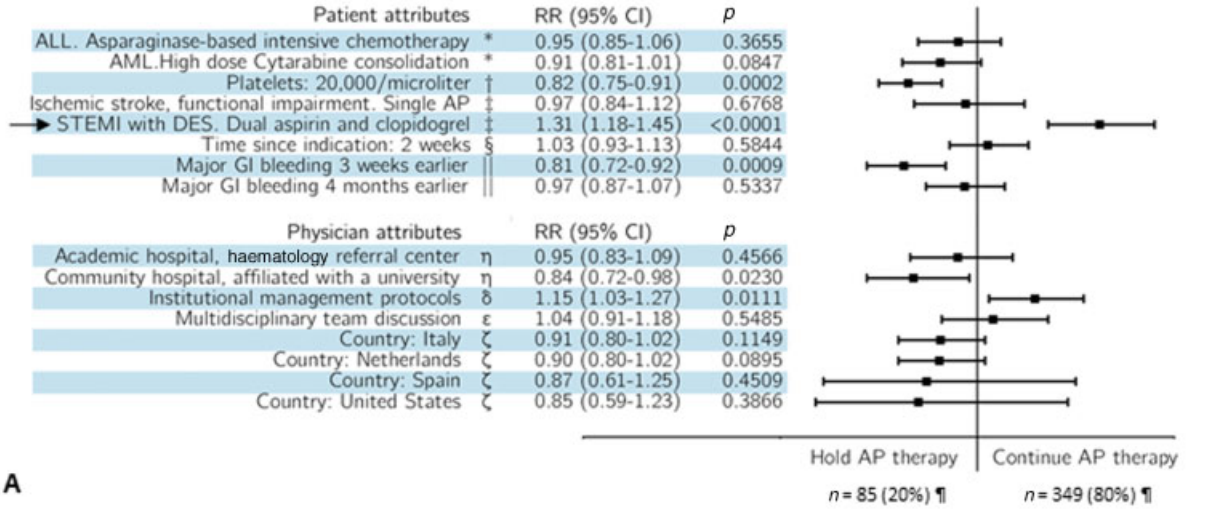
►**Table 1** shows the participants' demographics, practice setting and practice patterns. Briefly, 60 (41%) reported expertise in thrombosis, 122 (84%) were senior physicians and 134 (80%) worked at academic medical centres. Physicians estimated seeing a median of 5 patients (interquartile range [IQR] = 8) with thrombocytopaenia and either APT or anticoagulation per month. Institutional protocols guiding management of these patients were reported by 56 (39%) of all physicians, by 31/44 (71%) Dutch doctors, by 13/43 (28%) Israeli physicians and by 9/48 (19%) Italian participants.

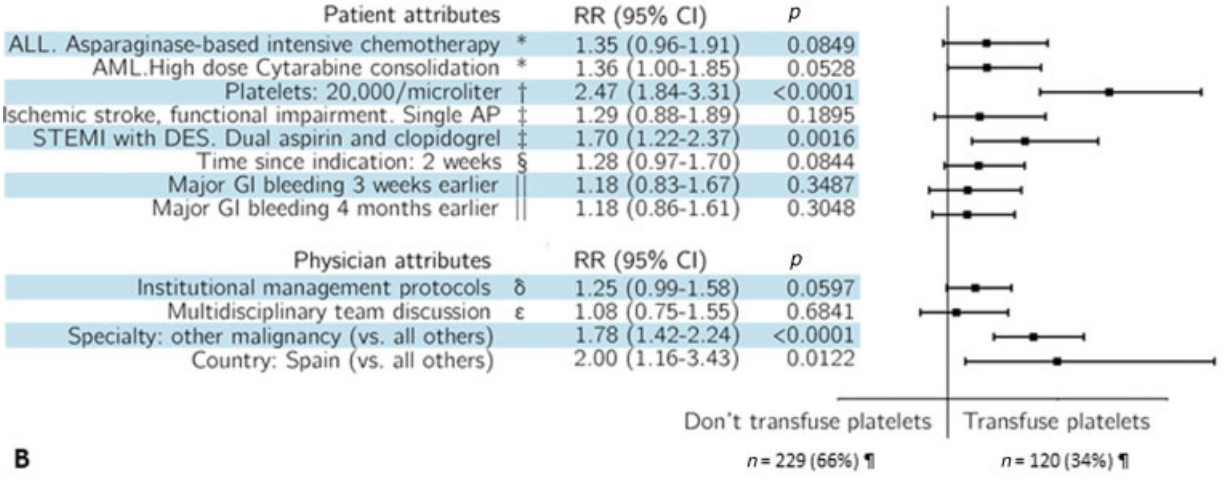
Case Vignettes

In total, management and bleeding/thrombotic risk were reported for 434 case vignettes amounting to 2.99 cases per physician, on average. Only one physician did not complete the survey. Physicians took a median of 94 seconds (IQR, 87) to complete each vignette. In these thrombocytopaenic cases, continuing the same APT without platelet transfusion support was the management strategy selected most often, chosen by 104 (72%) of the 145 physicians at least once. This was followed by continuing APT with platelet transfusion support ($n = 74$; 51%) and holding all APT ($n = 61$; 42%).

Patient and Physician Variables Associated with Management

►**Supplementary Table S2** (available in the online version) shows the distribution of management choices for each of the primary management steps (A→B→C), as well as the





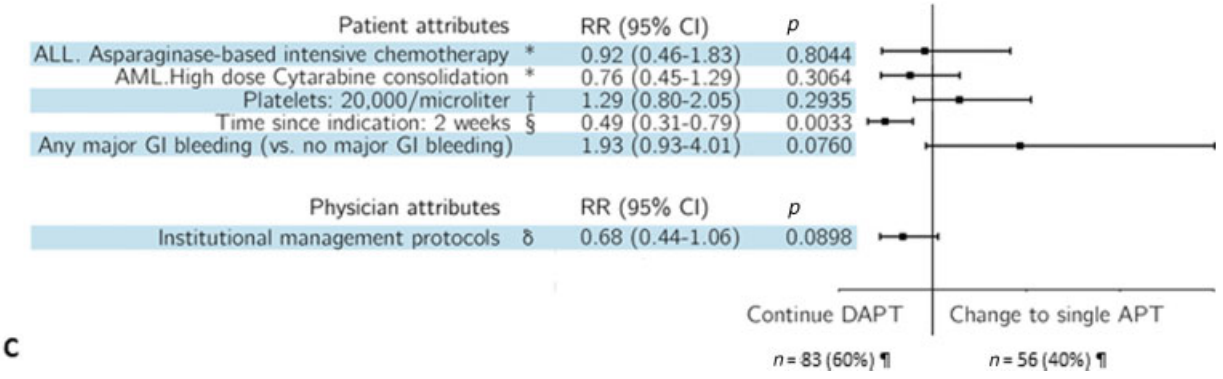


Fig. 2 Forest plots with RRs (95% confidence interval [CI], *p* value), derived from a cluster robust Poisson regression model, for selecting a management strategy (over the other) for each patient or physician variable in comparison to reference variables. Reference variables are signified by symbols adjacent to each variable. Plots A, B and C show management steps A, B and C, respectively. The arrow to the left of plot A denotes an example discussed in the article. The patient and physician attributes are detailed in ►**Fig. 1** and ►**Table 1**, respectively. * DLBCL, R-CHOP treatment. † 40,000/μL. ‡ Unstable angina (no stent), single AP therapy. § 2 months. || No prior GI bleeding. η Non-academic community hospital. δ No institutional management protocols. ε No multidisciplinary discussion of cases. ζ Israel. ¶ Number of cases in which the management strategy was selected (%). Abbreviations: AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; AP, anti-platelet; APT, anti-platelet therapy; DAPT, dual anti-platelet therapy; DES, drug-eluting stent; DLBCL, diffuse large B cell lymphoma; GI, gastrointestinal; R-CHOP, rituximab cyclophosphamide doxorubicin vincristine prednisone; RR, relative risk; STEMI, ST elevation myocardial infarction.

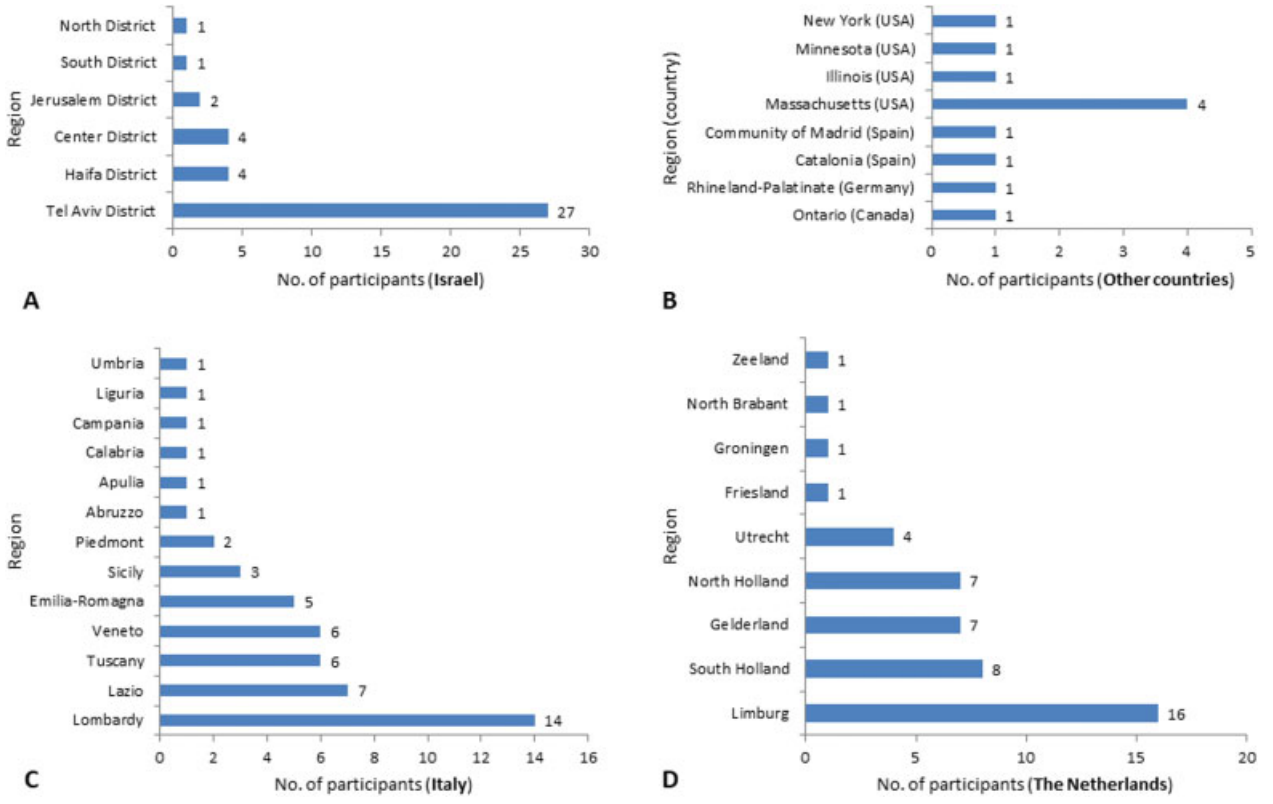


Fig. 3 Distribution of participants across regions in each country (panel **A**, Israel; panel **B**, other countries; panel **C**, Italy; panel **D**, The Netherlands). This distribution was estimated using the IP addresses at which the questionnaires were answered. IP, internet protocol; USA, United States of America.

unadjusted RRs for choosing one management strategy over the other, stratified by levels within a given attribute. ►**Fig. 2** shows forest plots with adjusted RRs (95% CI), derived from the multivariate model, for choosing one management strategy over the other at each step, for every variable compared with its reference. Although all patient and physician variables were considered during modelling, the plots in ►**Fig. 2** depict only the variables that remained in the final multivariable models.

Continue APT versus Hold

Physicians elected to continue APT (± platelet transfusion or change in APT regimen) in 349 cases (80%), while APT was held in 85 (20%) (step A; ►**Fig. 2A**). DAPT due to ST elevation MI (STEMI) and a drug-eluting stent (DES), makes it 31% more likely that a physician would continue APT than when single APT was used for conservatively treated unstable angina (95% CI: 1.18–1.45), as marked by an arrow in ►**Fig. 2A**. In addition, continuing APT was 15% more likely when there were institutional protocols guiding management (RR 1.15, 95% CI: 1.03–1.27). On the other hand, holding all APT was preferred over continuing if platelets were 20,000/μL (vs. 40,000/μL), in case of major gastrointestinal (GI) bleeding 3 weeks earlier (vs. none), and when the physician worked at a university-affiliated community hospital (vs. non-academic community hospital).

Platelet Transfusion Support

Platelet transfusion was chosen to support APT in 120 cases (34%) and not used in 229 cases (step B; ►**Fig. 2B**). The platelet transfusion target (step B.1) was 30,000/μL in 46 cases (43%), 50,000/μL in 62 (57%) and not pre-defined in 12 (10%) cases. Platelet transfusion support (with any target) was preferred if platelet counts were lower (20,000/μL vs. 40,000/μL), in case of DAPT due to STEMI with DES (vs. unstable angina with single APT), when the physician had expertise in general malignant haematology (vs. all other disciplines) and among Spanish physicians (vs. all others). In addition, there were borderline significant trends towards platelet transfusion support in cases with acute myeloid leukaemia receiving high-dose cytarabine consolidation therapy (RR 1.36, 95% CI: 1.00–1.85) and when there were institutional management protocols (RR 1.25, 95% CI: 0.99–1.58). A sensitivity analysis of cases with single APT ($n = 207$), showed the same proportion of platelet transfusion support and similar associations with case and physician variables (►**Supplementary Figs. S4**, available in the online version).

Changing DAPT to Single APT

There were 145 cases with DAPT (aspirin and clopidogrel) due to STEMI. Both anti-platelet drugs were held in 6 (4%) cases, while DAPT was continued with platelet transfusion support in 51 (35%) cases and without support in 32 (22%). Furthermore,

Table 1 Characteristics of participating physicians

Category	Variable group	Level	Number of participants (%) ($n = 145$)
Physician demographics	Rank	Senior physician with management role	48 (33)
		Senior physician	74 (51)
		Resident	9 (6)
		Fellow[a]	14 (10)
	Primary clinical expertise	General haematology	30 (21)
		Leukaemia	3 (2)
		Other malignant haematology[a]	25 (17)
		Stem cell transplantation	5 (4)
		Thrombosis	60 (41)
		Transfusion medicine	17 (12)
		Other	5 (4)
	Years of clinical experience	*Median, y (IQR)*	*15 (18)*
	Estimated number of patients[b] seen per month	*Median (IQR)*	*5 (8)*
Practice setting	Country	Israel[a]	46 (32)
		Italy	48 (33)
		The Netherlands	44 (30)
		Other[d]	7 (5)
	Hospital type	Academic tertiary referral centre	73 (50)
		Academic community hospital	49 (34)
		Non-academic community hospital[a]	23 (16)
	Institutional guidelines[c]	Yes	56 (39)
		No[a]	89 (61)
Practice patterns	Multidisciplinary discussion before deciding patient[b] management	Yes	116 (80)
		No[a]	29 (20)
	Discussion with patient[b] prior management decision	Yes, and influences management	97 (67)
		Yes, but does not influence management	38 (26)
		No[a]	10 (7)

Abbreviation: IQR, interquartile range.
Note: This table shows the demographics, practice setting and relevant practice patterns of the physicians participating in this survey.
[a]This was the reference level for statistical comparisons within this categorical variable group.
[b]Patients with thrombocytopaenia and an indication for anticoagulation or anti-platelet medication.
[c]Guidelines for managing patients with thrombocytopaenia and an indication for anticoagulation or anti-platelet medication.
[d]This included physicians from the United States (3) and Spain (4).

56 (39%) cases had DAPT changed to single APT with aspirin ($n = 20$) or clopidogrel ($n = 36$). Among the DAPT cases continuing APT (step C; ►**Fig. 2C**), continuing DAPT was preferred over single APT, when the DAPT indication was 2 weeks earlier (vs. 2 months earlier). In addition, there was a non-significant trend towards changing to single APT in case of any prior major GI bleeding (RR 1.93, 95% CI: 0.93–4.01).

Subjective Assessment of Bleeding and Thrombotic Risk

Across all cases, physicians subjectively assessed a mean (±standard deviation) bleeding risk of 5.8/10 (±2) and a mean thrombotic risk of 6/10 (±2).

Associations with Management

The RRs (95% CI) for choosing one management strategy over the other for increasing bleeding and thrombotic risks are shown in ►**Table 2**. Increasing thrombotic risk correlated only with continuing APT over holding (step A), whereby each increase in perceived thrombotic risk by one unit increased the probability that physicians would continue APT by 8%. Stepwise, increasing bleeding risk was associated with holding all APT (step A), platelet transfusion support (step B), a platelet transfusion target of 50,000/μL over 30,000/μL (step B.1) and with changing DAPT to single APT over continuing DAPT (step C).

Table 2 Associations between increasing bleeding or thrombotic risk[a] and management choice

Step	Management choice	Increasing bleeding risk, RR (95% CI)[a]	Increasing thrombotic risk, RR (95% CI)[a]
A	Continue any APT[b] (*over holding all*)	0.93 (0.91–0.95)[f]	1.08 (1.05–1.10)[f]
B[c]	Platelet transfusion support (*over no support*)	1.09 (1.02–1.17)[g]	1.05 (0.98–1.13)
B.1[d]	Platelet transfusion target = 30,000/μL (*over 50,000/μL*)	0.89 (0.80–0.99)[g]	0.96 (0.86–1.07)
C[e]	Change to single APT (*over continuing DAPT*)	1.22 (1.08–1.37)[g]	0.93 (0.85–1.02)

Abbreviations: APT, anti-platelet therapy; CI, confidence interval; DAPT, dual anti-platelet therapy; RR, relative risk.
Note: This table shows the relative risk for selecting a specific management strategy (over the other) by increasing bleeding or thrombotic risk.
[a]Subjective physician assessment of bleeding and thrombotic risk associated with a given case vignette, using separate scales of 0 (negligible risk of thrombosis/bleeding) to 10 (highest). RRs indicate the change in probability of the outcome (e.g. continuing APT) per unit increase in the scale (e.g. going from a bleeding risk of 6/10 to 7/10 decreases the probability of continuing APT by 7% and increases the probability of platelet transfusion support by 9%).
[b]With or without platelet transfusion support or change in APT regimen.
[c]When any APT was continued (all cases).
[d]When platelets were transfused to support any APT.
[e]In cases with dual APT, when APT was continued.
[f]$p < 0.0001$.
[g]$p < 0.05$.

Variability between Physicians

►**Fig. 4** depicts the relationship between physician-assessed bleeding and thrombotic risk selected by individual physicians and management (steps A and B). At step A, the change in management preference occurred at bleeding risk scores of 7 to 9 and at thrombotic risk scores of approximately 1 to 5. For all plots, the differing intercepts indicate that the average response to a given risk differs by physician. However, the rate at which a given management strategy is pursued is virtually the same for all physicians, since the slopes are similar.

Discussion

To the best of our knowledge, this clinical vignette-based experiment provides the first comprehensive data on the management of patients with thrombocytopaenia, haematological malignancy and an indication for APT, shedding light on current practice. Haematologists and thrombosis specialists reported encountering patients with APT or anticoagulation on a weekly basis, emphasizing that this is not a rare scenario, as shown in a prior cohort study of thrombocytopaenic cancer patients.[3]

In our study, 80% of all cases had APT continued. Overall, clinicians were more likely to discontinue APT if they considered the bleeding risk to be high and to continue if the thrombotic risk was considered to be high. Most of the treatment discontinuations occurred in cases receiving single APT (due to prior unstable angina or ischaemic stroke), while only a handful of DAPT cases (due to STEMI) had both anti-platelet drugs held. In contrast, in prior cohort studies only 34 to 43% of patients with ACS received aspirin therapy in this setting.[12,16,25] The greater tendency to continue aspirin in our study appears to be a reasonable approach in light of recent data showing that aspirin use was associated with increased survival and decreased cardiovascular mortality without an increase in major bleeding in patients with acute MI, thrombocytopaenia (< 50,000/μL) and haematological malignancy.[12]

DAPT was continued in more than half of the STEMI cases. Of note, 39% had DAPT changed to single APT, even though only 2 weeks or 2 months had passed since the STEMI. This represents early discontinuation of DAPT, since DAPT is indicated for at least 3 months after STEMI with DES in patients at a very high risk of bleeding.[26] The high rate of changing to single APT may be down to concern over an increased risk of bleeding, as suggested by our study findings. Importantly, sub-optimal use of DAPT may theoretically contribute towards the adverse cardiovascular outcomes observed in cancer patients with STEMI treated with primary PCI.[9] Traditionally, these patients have had a higher rate of bare-metal stent implantation,[9] possibly to shorten the duration of DAPT. This should no longer be a consideration since there are superior outcomes with second-generation DES in patients at a high risk of bleeding (including thrombocytopaenia).[27,28]

In cancer, prophylactic platelet transfusions are generally considered when platelet counts are below 10,000/μL.[29] We demonstrated that physicians used platelet transfusions at increased thresholds to support APT in as many as one third of cases, especially when the bleeding risk increases. There was no clear preference towards either of the transfusion targets in our survey (i.e. 50,000/μL or 30,000/μL). Potential risks of increased transfusion targets include depletion of platelet supplies, increased costs, refractoriness to platelet transfusion and adverse effects, such as arterial and venous thrombosis, volume overload and non-haemolytic febrile transfusion reactions.[30–33] Furthermore, increased transfusion targets are often not met, resulting in high rates of anticoagulation discontinuation.[30,32] Importantly, there are no data on the efficacy of this transfusion strategy. Of note, researchers recently demonstrated multiple functional platelet abnormalities in chemotherapy-induced thrombocytopaenia, which can be partially corrected by platelet

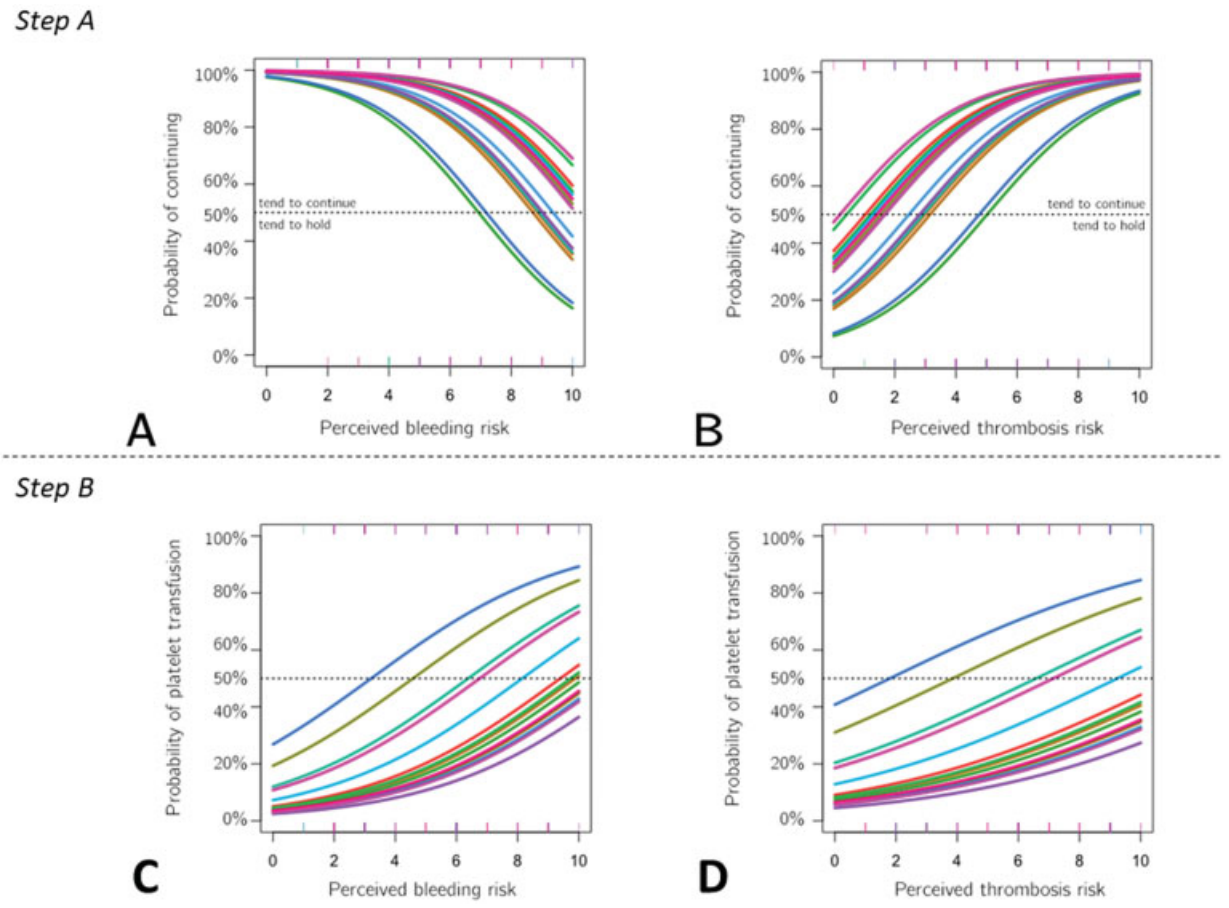


Fig. 4 Physician-assessed bleeding and thrombosis risks and their impact on clinical decision making in this case vignette study. Plots **A** and **B** show the probability of *continuing any AP medication versus holding* (*Y* axis), according to the bleeding (**A**) and thrombotic (**B**) risks assessed by physicians on a scale of 0 to 10 (*X* axis). Plots **C** and **D** show the probability of *transfusing platelets or modifying the AP regimen versus making no change* (*Y* axis), correlated with the bleeding (**C**) and thrombotic (**D**) risks. Each curve represents all the cases answered by one physician. Fifteen curves are shown in each panel, representing the full spectrum of variability between physicians. These curves are equidistantly distributed across the full range of risk assessment percentiles. Abbreviation: AP, anti-platelet.

transfusion.[34] It is, however, not known how these abnormalities and restoring platelet function impact bleeding and thrombosis in this setting, and how APT affects this equation. Taken together, this transfusion strategy warrants investigation,[35] considering its frequent use and the lack of data on its safety and efficacy.

Multiple clinical variables were associated with management choices in this setting, highlighting the complexity of these decisions. These include platelet count, indication for APT, time since the indication and prior major GI bleeding. Strategies aimed at mitigating the bleeding risk (i.e. holding APT or transfusing platelets) were more likely when platelet counts were 20,000/µL compared with 40,000/µL. Nonetheless, we could not determine the exact platelet threshold for management changes. It is also worth mentioning that individual platelet counts between 10,000/µL and 50,000/µL are not clearly associated with bleeding risk in thrombocytopaenic cancer patients without APT.[36]

In case of recent major GI bleeding (i.e. 3 weeks earlier), physicians were more likely to mitigate the bleeding risk by holding APT. In addition, there was a non-significant trend towards changing DAPT to single APT when there was prior major GI bleeding. This is in line with studies demonstrating that a history of previous bleeding is a risk factor for bleeding in patients with APT, in the general population.[4–6] The type of indication and anti-platelet regimen also affected management: in cases with DAPT for STEMI and DES, continuing APT was more likely than in unstable angina without PCI. Furthermore, STEMI patients receiving DAPT were also more likely to be given platelet transfusion support. This is clinically plausible, since outcomes are worse after STEMI than after unstable angina,[37] while DAPT is associated with increased risks of bleeding.[38–40]

Regarding the time since the initial indication for APT, there was no difference in continuing APT (over holding) between the two time points selected for evaluation in this study (2 weeks vs. 2 months). However, in STEMI cases, continuing DAPT (over switching to single APT) was more likely when the ischaemic event occurred 2 weeks earlier (vs. 2 months). A more aggressive approach to APT is reasonable in the acute period after STEMI, compared with the sub-acute and chronic periods, due to different thrombotic risk profiles.[13,17,18,27] While guidelines recommend at least 3 months of DAPT after DES implantation in patients at very high risk of bleeding,[26] researchers have hypothesized shorter DAPT durations in thrombocytopaenic patients.[13]

Of note, APT is indicated in acute and chronic ischaemic arterial disease. However, the cases in our study cover acute and sub-acute, but not chronic, ischaemic arterial disease, since this was considered the most controversial and high-risk period. Therefore, the management of chronic ischaemic arterial disease remains unclear. This will be addressed by an on-going study which does include this patient group.[35] Importantly, patterns of anti-thrombotic medication use may be influenced by emerging data on new indications for anti-thrombotic drugs. Based on the findings of the COMPASS trial[41] and similar smaller trials, rivaroxaban (2.5 mg twice daily in combination with aspirin) was recently approved by the U.S. Food and Drug Administration for reducing the risk for major cardiovascular events in patients with chronic coronary artery disease or peripheral artery disease. How physicians would approach management of this regimen in thrombocytopaenia is unknown. In addition, the findings of the COMPASS trial are hypothesis-generating for scenarios in which anticoagulation dose reduction may be considered, such as thrombocytopaenia, since low rivaroxaban doses had clinical effects with a favourable safety profile.

Our study suggests that subjectively assessed bleeding risk is a universal driver of management decisions while thrombotic risk only affects one management choice. In view of these associations, studies are needed to determine whether bleeding complications affect clinical outcomes more than thrombotic complications do.

Another important finding is that practice setting (i.e. country, having institutional protocols guiding management, type of hospital) and physician demographics (i.e. primary clinical expertise) influenced management choices. Of note, the interactions between these variables were accounted for by the multivariate analysis. For instance, institutional protocols guiding management of these patients were more common in the Netherlands than in Italy and Israel. Of the three primary study centres, only the Dutch centre had an institutional protocol which is detailed in ►**Supplementary Table S3** (available in the online version). Details on the protocols at the other participating centres were not available, because of the anonymous design. We also showed that each physician manages a given self-assessed bleeding and thrombotic risk differently.

This variability in practice emphasizes that clinical guidelines are needed to streamline practice, within countries and institutions or even across countries. These guidelines should address the clinical factors identified in our study since they are clearly considered by physicians confronted with such cases. In addition, most physicians, but not all, indicated that their management decision would be made after a discussion with a multidisciplinary team. While the utility of such a discussion is not known, it should be encouraged given the evident complexity of these decisions, the lack of evidence and since the case manager during thrombocytopaenia is usually a haematologist while the anti-platelet medication is often prescribed by a neurologist or cardiologist.

This study has several unique strengths. The sample included physicians with a wide range of clinical expertise from different types of hospitals across at least 36 geographical regions. The methodology enabled us to provide estimates on the magnitude and statistical significance of the effect that each factor has on management choice. Moreover, the multivariate analysis accounts for associations between variables, while the mixed effects models were useful to visualize the degree of inter-physician variance. Importantly, our study has no clinically implausible findings, supporting the validity and reliability of the study findings.

There are several limitations that warrant discussion. *First*, the management process was assessed in an artificial setting and not with real patients. However, considering the lack of patient data and the rigorous design of the study, we feel that this is the best available evidence on current practice. Actually, this study was a preparatory phase in planning a prospective observational study in this field, which is currently recruiting patients.[35] Observational studies should adjust for the clinical variables associated with management in the current study, since these variables can confound the effect of management on major bleeding or thrombosis. *Second*, we can only discuss the selected variables and management strategies that were chosen based on interviews with a panel of experienced physicians and a literature review. Several variables identified as predictors of bleeding in patients without thrombocytopaenia and cancer were not evaluated, such as older age, female sex, renal failure and low on-treatment platelet reactivity.[42] It is reasonable to assume that they have an impact on management as well. However, we placed an emphasis on cancer-related variables in this study, and incorporating these additional variables in the cases would have created too much variability and an unfeasible sample size. These clinical variables (age, sex, renal function) were nonetheless included as three of the five case constants, meaning that they were the same across all cases and would not affect decisions. In addition, allogeneic haematopoietic stem cell transplantation, which carries a high bleeding risk, was not selected as a level in this study.[36] *Third*, the management choices reported by physicians may not reflect actual practice. However, the use of discrete choices (due to changes in multiple variables from case to case) and the survey's anonymous nature, minimize the potential for this bias. *Fourth*, only 16% of the target population answered the survey, potentially affecting the generalizability of the study. We could not evaluate selection bias since demographic data on the target population were not available. The potential of sampling and selection bias is partially reduced by incorporating multiple physician demographics and practice settings (shown in ►**Table 1**) into the multivariate model. Nonetheless, there may be residual confounding by variables that were not considered. Accordingly, the results may not be generalizable to all countries and practice settings. *Last*, the target population included haematologists, thrombosis specialists and specialists in transfusion medicine but not cardiologists and stroke physicians who are often consulted in this context and, in some instances, the primary case managers. This means that the factors driving management by cardiologists and stroke physicians remain unknown and need to be addressed by future studies.

In conclusion, the management of thrombocytopaenic patients with haematological malignancy and APT is affected by platelet count, APT indication, time since indication and prior GI bleeding, as well as physician demographics and practice setting. APT is usually continued, and platelet transfusions are frequently chosen to support APT. While most management strategies appeared reasonable, some were debatable, underlining the need for on-going research and consistent guidelines.

What is known about this topic?

- Anti-platelet therapy (APT), prescribed as secondary prevention for cardiovascular events, is frequently encountered in cancer patients. Thrombocytopaenia complicates the management of APT.
- Evidence is scarce but aspirin appears to increases survival, without increasing bleeding in thrombocytopaenic cancer patients with acute coronary syndrome.
- Aspirin was used in less than half of patients in these studies. Further information on current practice is lacking.

What does this paper add?

- In this case-vignette study, 145 haematologists and thrombosis specialists reported continuing APT in most of the cases with haematological malignancy, platelets $< 50{,}000/\mu L$ and unstable angina, ST elevation myocardial infarction or ischaemic stroke. Platelet transfusions were frequently chosen to support APT, although no evidence supports this practice.
- APT management is affected by platelet count, APT indication, time since the arterial event and prior gastrointestinal bleeding. There is significant variability in reported practice since field of expertise, country of practice, type of hospital and institutional protocols also influenced management.
- This study provides a framework of reasonable decisions. These patient variables should be addressed in guidelines and future studies assessing management.

Conflict of Interest
None declared.

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